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April 6, 2015

Ms. Michelle Arsenault
National Organic Standards Board
USDA-AMS-NOP
1400 Independence Ave. SW
Room 2648-S, Mail Stop 0268
Washington, DC 20250-0268

Re. LS: Xylazine, Tolazoline, and Butorphanol

These comments to the National Organic Standards Board (NOSB) on its Spring 2015 agenda are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and groups around the world.

The three livestock drugs appear to be listed for uses not allowed by law.

Xylazine and Tolazoline

Current listings

§205.603

(22) Tolazoline (CAS #-59-98-3)—federal law restricts this drug to use by or on the lawful written or oral order of a licensed veterinarian, in full compliance with the AMDUCA and 21 CFR part 530 of the Food and Drug Administration regulations. Also, for use under 7 CFR part 205, the NOP requires:

- (i) Use by or on the lawful written order of a licensed veterinarian;
- (ii) Use only to reverse the effects of sedation and analgesia caused by Xylazine; and
- (iii) A meat withdrawal period of at least 8 days after administering to livestock intended for slaughter; and a milk discard period of at least 4 days after administering to dairy animals.

(23) Xylazine (CAS #-7361-61-7)—federal law restricts this drug to use by or on the lawful written or oral order of a licensed veterinarian, in full compliance with the AMDUCA and 21 CFR part 530 of the Food and Drug Administration regulations. Also, for use under 7 CFR part 205, the NOP requires:

- (i) Use by or on the lawful written order of a licensed veterinarian;
- (ii) The existence of an emergency; and
- (iii) A meat withdrawal period of at least 8 days after administering to livestock intended for slaughter; and a milk discard period of at least 4 days after administering to dairy animals.

Xylazine is used in conjunction with Tolazoline. Xylazine is used as a sedative, analgesic (pain killer) and muscle relaxant in veterinary medicine. Tolazoline is used to reverse the effects of Xylazine.

Xylazine interacts with other tranquilizers, analgesics, and anesthetics.¹ It impairs the effectiveness of anticonvulsants.² Tolazoline has a number of interactions with other drugs.³ A metabolite of xylazine, 2,6-xylidine, is genotoxic and carcinogenic.⁴ “Numerous pharmacological side-effects of xylazine have been observed in treated animals, including mydriasis, impairment of thermo-regulatory control, various effects on the cardiovascular system, acid-base balance and respiration, hyperglycaemia, and haematological and gastrointestinal effects. Cattle and sheep are approximately 10 times more sensitive to xylazine than horses, dogs and cats.”⁵

According to the TAP review, “There are in fact, many alternative *practices* available for many uses of xylazine.”⁶

FDA does not permit the use of xylazine in food-producing animals, and the NOP cannot overrule FDA’s ruling.⁷ The transcripts⁸ indicate that the NOSB was under the impression that xylazine could be used as an “off-label use.” FDA says, “The Animal Medicinal Drug Use Clarification Act of 1994 AMDUCA) permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions.”⁹ However, in this case, the FDA specifically said it is not to be used in food-producing animals. FDA regulations:

21 CFR §530.21 Prohibitions for food-producing animals.

(a) FDA may prohibit the extralabel use of an approved new animal or human drug or class of drugs in food-producing animals if FDA determines that:

(1) An acceptable analytical method needs to be established and such method has not been established or cannot be established; or

(2) The extralabel use of the drug or class of drugs presents a risk to the public health.

(b) A prohibition may be a general ban on the extralabel use of the drug or class of drugs or may be limited to a specific species, indication, dosage form, route of administration, or combination of factors.

According to the TAP review, “The FDA has approved xylazine hydrochloride for use as a veterinary anesthetic, and tolazoline hydrochloride as a reverser of xylazine, but in both cases,

¹ http://www.ccac.ca/en_training/niaut/vivaria/analgesia/xylazine.

² Właź, P., & Roliński, Z. (1996). Xylazine impairs the anticonvulsant activity of conventional antiepileptic drugs in mice. *Journal of Veterinary Medicine Series A*, 43(1-10), 495-500.

³ TAP, p.36.

⁴ TAP, p. 12.

⁵ TAP, p. 25.

⁶ TAP, p. 42.

⁷ FDA regulations at 21 CFR 522.2662(d)(2)(iii) and 21 CFR 522.2662(d)(3)(iii). OFPA §6519(c)(6)(B)

⁸ Transcript of September 2002 meeting, pages 568-578.

⁹ http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ActsRulesRegulations/ucm085377.htm#Extra-Label_Use.

use of these medications in ‘food-producing animals’ is specifically unapproved.” The FDA regulations state,

21 CFR §522.2662 (iii) *Limitations*. Do not use in domestic food-producing animals. Do not use in Cervidae less than 15 days before or during the hunting season.

An off-label use may be allowable in the absence of a specific prohibition, but since FDA does explicitly prohibit the use of xylazine in food-producing animals, it should be delisted. Since tolazoline is listed as an antidote to xylazine, it should also be removed from the National List.

Butorphanol

Current listing

§205.603(a) As disinfectants, sanitizer, and medical treatments as applicable.

(5) Butorphanol (CAS #-42408-82-2)—federal law restricts this drug to use by or on the lawful written or oral order of a licensed veterinarian, in full compliance with the AMDUCA and 21 CFR part 530 of the Food and Drug Administration regulations. Also, for use under 7 CFR part 205, the NOP requires:

- (i) Use by or on the lawful written order of a licensed veterinarian; and
- (ii) A meat withdrawal period of at least 42 days after administering to livestock intended for slaughter; and a milk discard period of at least 8 days after administering to dairy animals.

The TAP review was thorough with respect to the use of butorphanol as a drug, but information about impacts of butorphanol and its metabolites when excreted was missing. Since metabolites of the drug can cross the placenta and pass into the mammary gland and into milk, more information about the metabolites would be helpful. When petitioned, it was considered a safe and necessary option.

The TAP review said that butorphanol may interact with other medications, including tranquilizers, barbiturates, and antihistamines. If used with other central nervous system depressants, butorphanol may increase the central nervous system or respiratory depression of those drugs.¹⁰ Butorphanol and its metabolites are not considered toxic, but there are withdrawal periods to observe before using meat or milk.¹¹

The use of butorphanol also appears to be an extra-label use, and while the regulations are less clear than for xylazine, it appears that butorphanol is not permitted for use in food animals. 21 CFR §522.246 addresses the use of butorphanol in dogs, cats, and horses. Under horses, the following restriction is listed:

- (iii) *Limitations*. Do not use in horses intended for human consumption.

Therefore, we ask that the LS do two things with respect to butorphanol:

¹⁰ TAP, p. 18.

¹¹ TAP pp. 18, 25.

1. Find and present information about impacts of butorphanol and its metabolites when excreted; and
2. Get a determination from FDA regarding the legal use of butorphanol in food animals.

Thank you for your consideration of these comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Terry Shistar". The signature is fluid and cursive, with a long horizontal stroke at the end.

Terry Shistar, Ph.D.
Board of Directors